

Determination of personalized diabetes treatment plans using a two-delay model

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Abstract

Diabetes cases worldwide have risen steadily over the past decades, lending urgency to the search for more efficient, effective, and personalized ways to treat the disease. Current treatment strategies, however, may fail to maintain ultradian oscillations in blood glucose concentration, an important element of a healthy alimentary system. Building upon recent successes in mathematical modeling of the human glucose-insulin system, we show that both food intake and insulin therapy likely demand increasingly precise control over insulin sensitivity if oscillations at a healthy average glucose concentration are to be maintained. We then suggest guidelines and personalized treatment options for diabetic patients that maintain these oscillations. We show that for a type II diabetic, both blood glucose levels can be controlled and healthy oscillations maintained when the patient gets an hour of daily exercise and is placed on a combination of Metformin and sulfonylurea drugs. We note that insulin therapy and an additional hour of exercise will reduce the patient's need for sulfonylureas. Results of a modeling analysis suggest that a typical type I diabetic's blood glucose levels can be properly controlled with a constant insulin infusion between 0.45 and 0.7 $\mu\text{U}/\text{ml}\cdot\text{min}$. Lastly, we note that all suggested strategies rely on existing clinical techniques and established treatment measures, and so could potentially be of immediate use in the design of an artificial pancreas.

Keywords: Artificial pancreas, Blood glucose, Insulin sensitivity, Personalized medicine, Ultradian oscillations

1. Introduction

The number of cases of diabetes in the United States has doubled since 2000 and more than tripled since 1990, with current figures estimating about 25.8 million cases (Centers for Disease Control and Prevention [9, 10]). The term “diabetes” refers to a range of conditions, varying in origin and severity, characterized by chronic high levels of glucose in the blood, which can lead to peripheral neuropathy, cardiovascular disease, blindness, and even death (American Diabetes Association [2], Boulton [7], Kannel and McGee [18]). Type I diabetes is caused by autoimmune attack on the insulin-producing pancreatic β -cells. Its onset is largely dictated by genetic factors, and the disease is usually present from early in life (Daneman [12]). Type II diabetes is characterized by decreased sensitivity to insulin, making it more difficult for cells to utilize glucose and eventually impairing insulin secretion by pancreatic β -cells (Stumvoll et al. [28]). While generally less severe, Type II is also much more common and possesses many risk factors ranging from genetics to obesity. Each case is unique and no two people have the same ability to utilize glucose, the same insulin production rate, or the same lifestyle. With no known cure for diabetes, lifelong treatment is generally the only option. It is therefore of great importance for an individual's treatment plan to be tailor-made for his or her specific condition.

The American Diabetes Association (ADA) recommends a combination of diet, exercise, medication, and insulin therapy to treat diabetes. These treatments are used to lower blood glucose concentration (BGC) to a healthy

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level (American Diabetes Association [4]). However, another important factor is often overlooked: blood glucose levels in non-diabetic individuals also fluctuate by about 10% every two hours or so. These so-called *ultradian oscillations* (i.e., taking place multiple times each day) were first noted by Hansen in 1923, and various studies since have underlined their prominence and functional importance in regulating glucose concentration (Drozdov and Khanina [14], Hansen [17], Simon et al. [26, 27]). The root cause of these oscillations is not fully understood, though evidence suggests that delayed feedback between insulin-producing pancreatic β -cells and the liver may be a significant contributing factor Li et al. [20]. As these oscillations are natural and indicative of healthy insulin dynamics, any effective treatment strategy should aim to maintain these oscillations.

With these points in mind, our goal is to develop a systematic strategy to determine a personalized treatment plan for lowering a diabetic’s BCG to within the ADA-specified range (between 70 and 130 mg/dl before meals (American Diabetes Association [3])). This treatment plan should retain the ultradian glucose oscillations observed in healthy individuals and should rely on existing standard treatment measures, i.e. diet, exercise, insulin therapy, and/or medication. It should be straightforward enough to be programmed into a medical device such as an artificial pancreas. Finally, the information necessary to personalize the treatment plan should be readily available from existing clinical procedures. To accomplish these goals we will study a mathematical model of the human glucose-insulin system that explicitly accounts for the treatment methods proposed by the ADA. We present this model in Section 2. In Section 3 we identify the conditions under which a person’s BGC will reach an acceptable range and will oscillate. To illustrate how this method can be put into practice, we perform a hypothetical case study in Section 4, in which we set forth viable plans to treat a Type I and a Type II diabetic. We conclude with our results in Section 5 and propose areas for further research.

2. Model Presentation

We begin with a schematic model of the human glucose-insulin system, illustrated in Figure 1. In the human body, ingested food is converted to glucose, which fuels bodily functions and encourages the production of insulin. This insulin, in turn, slows down further glucose production to prevent a buildup of glucose in the blood stream. The model given by equations (1) and (2) mathematically describes this process.

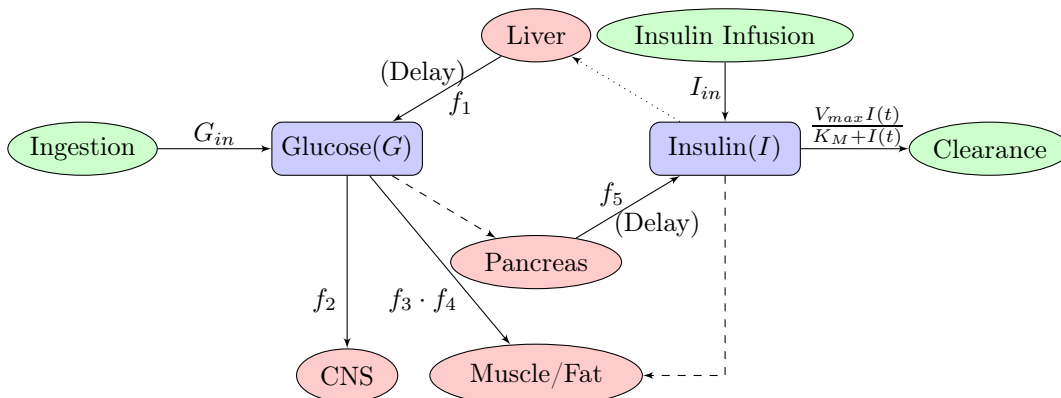


Figure 1: Schematic diagram of the human glucose-insulin system. Solid lines denote production/consumption of a substrate (glucose or insulin), dotted lines denote inhibition by a substrate, and dashed lines denote encouragement by a substrate. Ingested food is converted to glucose, which the body uses to fuel biological processes. Glucose also stimulates pancreatic β -cells to produce insulin, which in turn inhibits the liver’s production of glucose. The central nervous system (CNS) processes glucose without insulin, whereas insulin enhances glucose uptake by muscle and fat cells. Thus, when blood glucose levels are high, insulin is produced to stimulate glucose uptake and to slow the production of further glucose from the liver. When blood glucose levels are low, insulin is produced more slowly and the liver’s production of glucose speeds up. This feedback loop helps to keep a person’s blood glucose levels in a state of oscillatory homeostasis.

$$G' = G_{in} + f_1(I(t - \tau_2)) - f_2(G(t)) - \gamma[1 + s(m - m_b)]f_3(G(t))f_4(I(t)) \quad (1)$$

$$I' = I_{in} + \beta f_5(G(t - \tau_1)) - \frac{V_{max}I(t)}{K_M + I(t)} \quad (2)$$

For clarity, let us explain the links between the terms in Equations (1) and (2) and the processes depicted in Figure 1. We first note that glucose concentration (G) can increase via two pathways: (1) ingestion and (2) production by the liver (commonly called *hepatic production*). We first consider ingestion, for which we represent glucose intake rate by G_{in} . We make this term constant because, if it were instead periodic (as in the case of multiple daily meals), this periodicity would automatically induce ultradian glucose oscillations. Simon et al. [26] demonstrated that ultradian glucose oscillations exist in healthy individuals even when ingesting glucose at a constant rate, and we want to ensure that our model accounts for this behavior.

We next consider hepatic glucose production, denoted by $f_1(I(t - \tau_2))$. The equation for f_1 is given in Table 2 and its shape in Figure 2. Insulin inhibits hepatic production, so it makes sense that f_1 would be a decreasing function of insulin concentration. Furthermore, there is a well-documented time delay between when insulin reaches the liver and when the liver responds by adjusting glucose production rate (Li et al. [20]). We denote this delay as τ_2 , the amount of time (in minutes) required for a change in insulin concentration to affect hepatic glucose production.

Glucose concentration can also decrease via two pathways, namely (1) utilization by the central nervous system and (2) utilization by muscle and fat cells. Glucose utilization by the central nervous system (CNS) does not depend on insulin concentration; these cells will use all of the glucose available to them up to a threshold. We represent this behavior with f_2 , whose equation is given in Table 2 and shape in Figure 2. Muscle and fat cells, on the other hand, do rely on the presence of insulin to take up glucose; thus, we represent their consumption with the product $f_3(G(t)) \cdot f_4(I(t))$. Here we arrive at the first complication that diabetic illness introduces; the muscle and fat cells of type II diabetics are less sensitive to insulin, and thus cannot take up glucose from the blood stream as easily as a non-diabetic person's cells. The scaling factor γ accounts for this; γ can take values from 0 to 1, with 0 corresponding to no ability for muscle and fat cells to take up glucose, and 1 corresponding to a non-diabetic person's glucose uptake ability. Thus, lower values of γ correspond to more severe cases of diabetes. The additional factor, $[1 + s(m - m_b)]$, accounts for the positive effect of exercise on insulin sensitivity (Devlin [13]). Here, m corresponds to minutes of moderate to vigorous physical activity (MVPA) per day. 60 minutes per day of MVPA ($m_b = 60$) is considered average; any less than this decreases glucose tolerance and any more increases glucose tolerance, with the effect of exercise more significant for individuals with better baseline glucose tolerance (γ close to 1). Nelson et al. observed a decrease in insulin resistance corresponding to an increase in physical exercise; this data is well-modeled by the line $y = 1.9127 - 0.0072x$ (Nelson et al. [24]). The slope of this line, interpreted

Table 1: Parameter values for model equations (1) and (2)

Parameters	Units	Range	Meaning
β	—	0 – 1	Relative pancreatic β -cell function
γ	—	0 – 1	Relative insulin sensitivity
G_{in}	mg/dl·min	0 – 1.08	Glucose intake rate
I_{in}	$\mu\text{U}/\text{ml}\cdot\text{min}$	0 – 2	Insulin infusion rate
K_M	$\mu\text{U}/\text{ml}$	2300	Insulin degrading enzyme's half-saturation concentration
m	min	0-120	Daily minutes of physical activity
m_b	min	60	Baseline minutes of physical activity
s	1/min	0.0072	Rate of insulin sensitivity increase per minute of exercise
V_{max}	$\mu\text{U}/\text{ml}\cdot\text{min}$	150	Maximum insulin clearance rate

Table 2: Definitions of functions $f_1 - f_5$ from model equations (1) and (2). Parameter values are given in Table 3.

Modeling Term	Physiological Process
$f_1(I) = R_g / (1 + \exp(\alpha(I/V_p - C_5)))$	Hepatic glucose production
$f_2(G) = U_b(1 - \exp(-G/(C_2V_g)))$	CNS glucose utilization
$f_3(G) = G/(C_3V_g)$	Muscle/fat glucose utilization
$f_4(I) = U_0 + (U_m - U_0)/(1 + \exp(-\beta \ln(I/C_4(1/V_i + 1/(Et_i))))))$	Muscle/fat insulin uptake
$f_5(G) = R_m / (1 + \exp((C_1 - G/V_g)/a_1))$	Pancreatic insulin production

Table 3: Parameter values for functions $f_1 - f_5$ (from Li et al. [21], Sturis et al. [30], and Tolic et al. [31])

Parameters	Units	Values	Meaning
α	liter/mU	0.29	Scaling factor; sets hepatic sensitivity to changes in insulin
β	—	1.77	Scaling factor
a_1	mg/liter	300	Scaling factor; sets pancreatic sensitivity to changes in glucose
C_1	mg/liter	2000	Glucose concentration at which pancreas is most efficient
C_2	mg/liter	144	Scaling factor; sets CNS cell sensitivity to changes in glucose
C_3	mg/liter	1000	Scaling factor; sets muscle cell sensitivity to changes in glucose
C_4	mU/liter	80	Scaling factor; sets muscle cell sensitivity to changes in insulin
C_5	mU/liter	26	Insulin concentration at which liver is most efficient
E	liter/min	0.2	Insulin transport rate from plasma into cells
R_g	mg/min	180	Maximum hepatic glucose production rate
R_m	mU/min	210	Maximum pancreatic insulin production rate
t_i	min	100	Exponential time constant for intercellular insulin degradation
U_0	mg/min	40	Low-insulin limiting rate of muscular glucose consumption
U_b	mg/min	72	Maximum glucose utilization rate by brain and nerve cells
U_m	mg/min	940	High-insulin limiting rate of muscular glucose consumption
V_g	liter	10	Volume of the body into which glucose can diffuse
V_i	liter	11	Intercellular volume
V_p	liter	3	Volume of plasma in the body

as the percent increase in glucose tolerance for each additional minute of exercise, provides the rationale behind multiplying by $s = 0.0072$ in Equation (1).

Now let us justify the equation for insulin concentration, Equation (2). Like glucose, there are two pathways by which insulin concentration can increase: (1) insulin infusion and (2) pancreatic β -cell production. We let the insulin infusion I_{in} be a constant since periodic insulin infusion would only make sense if glucose intake were also periodic. We represent pancreatic β -cell production with the function $f_5(G(t - \tau_1))$, defined in Table 2 and with form given in Figure 2. As illustrated in the schematic diagram, elevated blood glucose encourages pancreatic insulin production. There is a delay before the pancreas can respond to changes in blood glucose, for which τ_1 accounts (Li et al. [20]).

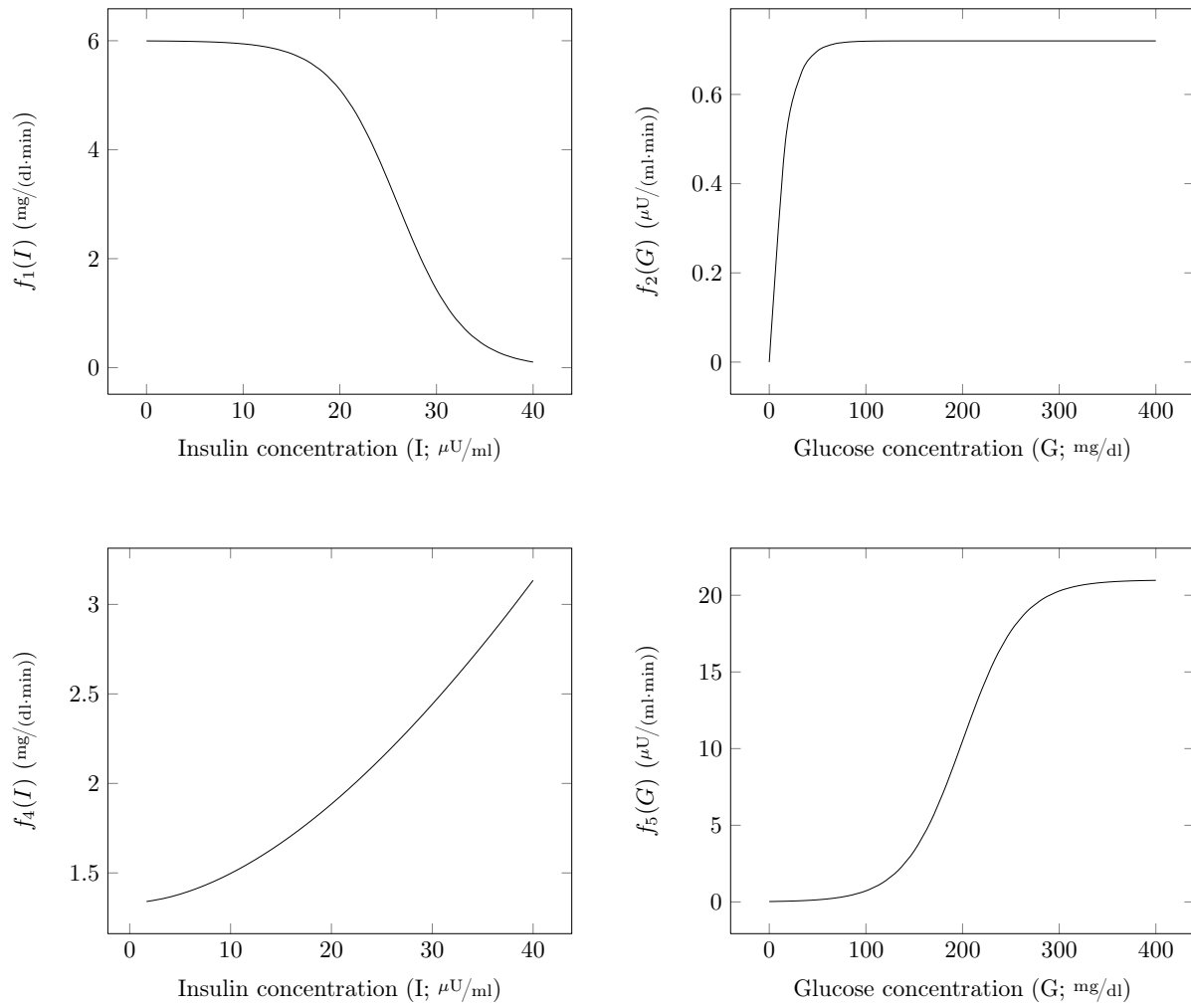
Finally, there is one significant way for insulin concentration to decrease, which is through metabolism by human insulin-degrading enzyme (IDE) (Authier et al. [5]). As an enzymatic reaction, we quantify insulin degradation with Michaelis-Menten kinetics using the term $\frac{V_{max}I(t)}{K_M + I(t)}$. Here, V_{max} is the maximum insulin clearance rate and K_M is the enzyme's half-saturation value (Wang et al. [32]).

3. Analysis

Since type I and type II diabetes differ so significantly in origin and in the type of therapy required, we will address them separately here, starting with the more prevalent type II.

3.1. Type II diabetes

To lay the groundwork to address our first two objectives, we consider the fasting case with no insulin therapy, i.e. $G_{in} = I_{in} = 0$. This corresponds to the conditions one would expect for an individual undergoing diagnostic

Figure 2: Functional forms of f_1 , f_2 , f_4 , and f_5 , from Li et al. [20]

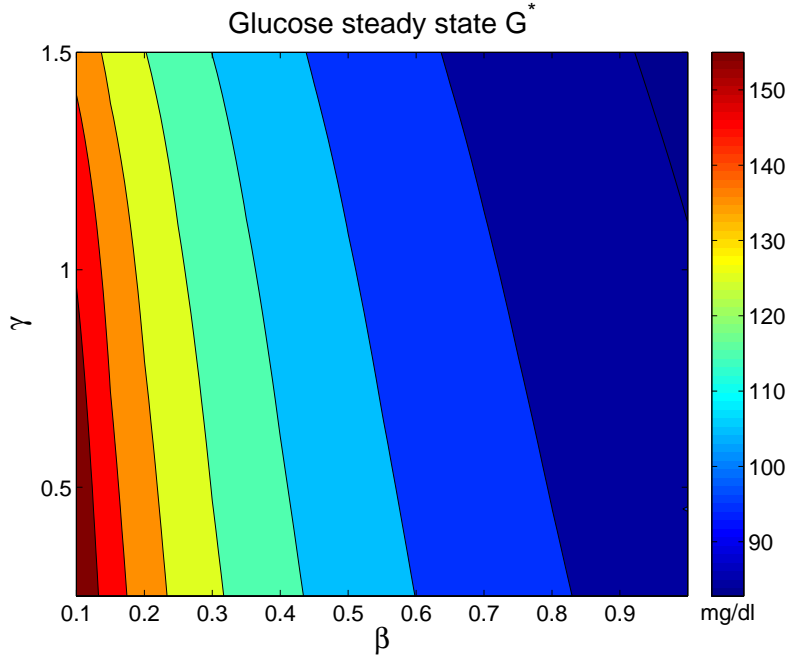


Figure 3: This figure depicts a person's steady state (average) blood glucose concentration as a function of pancreatic efficiency β and insulin sensitivity γ . It is apparent, according to the model, β affects blood glucose concentration much more strongly than γ . Also, small increases in β for a very poorly-functioning pancreas result in much more dramatic changes in blood glucose concentration than similar changes for an already well-functioning pancreas. Other model parameters are held fixed at: $\tau_1 = 5, \tau_2 = 15, m = 60, V_{max} = 150$, and $K_M = 2300$.

tests for diabetes, which are normally done after a fast of at least eight hours (American Diabetes Association [4]). We will first demonstrate how to determine an individual's steady state (or average) BGC, and will then show how to determine whether that person's glucose concentration oscillates.

In order to estimate the patient's average BGC we calculate the system's steady state, setting $G' = I' = 0$, $G(t) = G(t - \tau_1) = G^*$, and $I(t) = I(t - \tau_2) = I^*$. The constants G^* and I^* are the glucose and insulin steady states, respectively; all that remains is to solve for them. Since G and I arise in functions $f_1 - f_5$ as exponents, bases of exponents, and linear terms, it is very difficult to solve for the steady states G^* and I^* analytically. We instead do so numerically using the default Trust Region algorithm implemented in MATLAB's **fsolve** function. Figure 3 depicts solutions of the glucose steady state for varying β and γ , with all other parameters ($\tau_1, \tau_2, V_{max}, K_M, m$) held constant. It is immediately apparent from Figure 3 that pancreatic efficiency β is much more important than insulin sensitivity γ for determining a patient's average BGC. As expected, increasing either β or γ will lead to a lower BGC.

Now we would like to determine when a person's glucose concentration will oscillate. To do so, we linearize the model with respect to the substrates (G and I) about the steady state, and then find which parameter values yield eigenvalues with real part in the positive half-plane. The linearization gives three Jacobian matrices:

$$J_0 = \begin{bmatrix} -f'_2(G^*) - \gamma[1 + 0.0072(m - 60)]f'_3(G^*)f_4(I^*) & -\gamma[1 + 0.0072(m - 60)]f_3(G^*)f'_4(I^*) \\ 0 & \frac{V_{max}K_M}{(K_M + I^*)^2} \end{bmatrix}$$

$$J_1 = \begin{bmatrix} 0 & 0 \\ \beta f'_5(G^*) & 0 \end{bmatrix}$$

$$J_2 = \begin{bmatrix} 0 & f'_1(I^*) \\ 0 & 0 \end{bmatrix}.$$

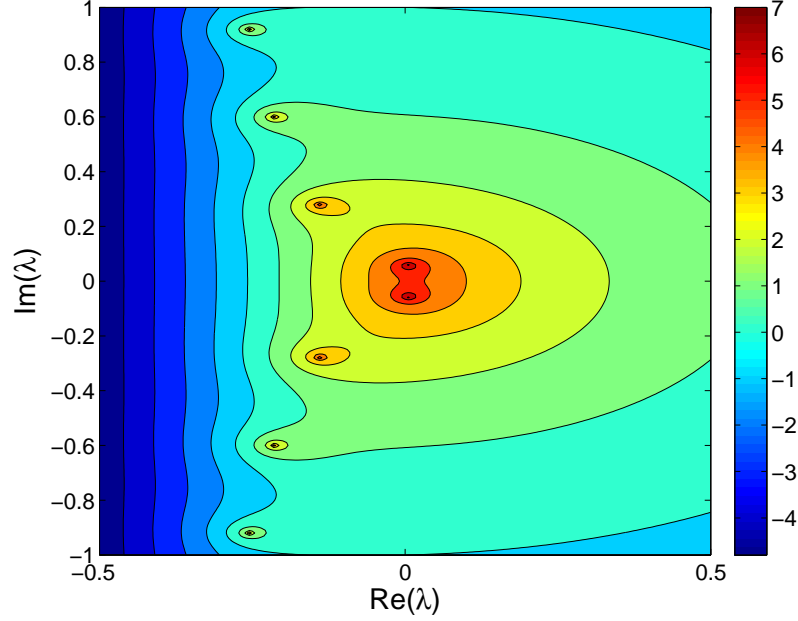


Figure 4: Contour plot of the logged-inverse of the determinant given by the left-hand side of Equation 3. The poles indicate the eigenvalues of the linearized system. These eigenvalues correspond to a non-diabetic individual, with $\tau_1 = 5$, $\tau_2 = 15$, $\beta = 1$, $\gamma = 1$, $m = 60$, $V_{max} = 150$, and $K_M = 2300$. Note that the dominant (rightmost) eigenvalues lie in the positive half-plane, indicating stable oscillations in blood glucose concentration.

The linear system is then

$$\begin{pmatrix} G(t) \\ I(t) \end{pmatrix}' = J_0 \begin{pmatrix} G(t) \\ I(t) \end{pmatrix} + J_1 \begin{pmatrix} G(t - \tau_1) \\ I(t - \tau_1) \end{pmatrix} + J_2 \begin{pmatrix} G(t - \tau_2) \\ I(t - \tau_2) \end{pmatrix}$$

Assuming solutions of the form $e^{\lambda t}$, we arrive at the following eigenvalue equation:

$$|J_0 + e^{-\lambda\tau_1} J_1 + e^{-\lambda\tau_2} J_2 - \lambda \mathbf{I}| = 0 \quad (3)$$

Plotting the inverse of this determinant and looking for poles allows us to identify which complex values of λ solve this equation and thus are eigenvalues. Figure 4 provides an example contour plot of this determinant-inverse using parameter values for a non-diabetic individual. Note that, as expected, the dominant (rightmost) eigenvalues lie in the positive half plane, indicating stable blood glucose oscillations. The eigenvalues move as the model parameters change, with increasing values of β and decreasing values of γ tending to induce a leftward shift in the eigenvalues. The dominant eigenvalues eventually cross the imaginary axis into the negative real half-plane, indicating the disappearance of ultradian glucose oscillations. Figure 5 depicts just how the real part of the dominant eigenvalue changes for various pancreatic efficiencies (β) as a function of insulin sensitivity (γ).

We are now in a position to determine which parameter values give an overall healthy blood glucose profile, marked by oscillatory glucose oscillations in a moderate (80-120 mg/dl) range. In order to simplify our analysis, we note that we can combine the information given by γ and m into a single parameter $\kappa \equiv \gamma[1 + 0.0072(m - 60)]$ that describes a person's overall glucose uptake efficiency. The lowest physiologically possible value for κ occurs when $\gamma = m = 0$, for which $\kappa = 0$. A feasible upper value for κ occurs when $\gamma = 1$ and $m = 120$ (that is, two hours of moderate to vigorous physical activity daily, which seems reasonable for the most active individuals), giving $\kappa = 1.432$. We will assume that κ can range between 0 and 1.5.

First, we would like to determine which values of β and κ give steady state solutions between 80 and 120 mg/dl.

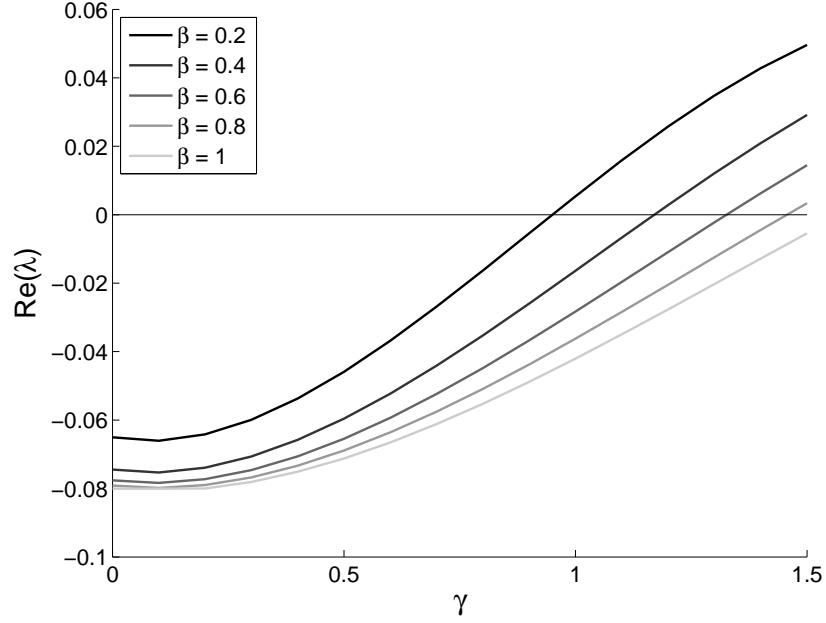


Figure 5: This plot indicates how the real part of the linearized system's dominant eigenvalue changes with insulin sensitivity γ for a few fixed values of β . The region below the $Re(\lambda) = 0$ line corresponds to a stable solution, while the region above corresponds to oscillatory solutions. It appears that higher values of both β and γ will tend to give rise to oscillatory solutions.

To do so, we note that, given the steady state values G^* and I^* , we can solve for the parameters κ and β :

$$\kappa = \frac{-f_2(G^*) + f_5(I^*)}{f_3(G^*)f_4(I^*)} \quad (4)$$

$$\beta = \frac{V_{max}I^*}{f_1(G^*)(K_m + I^*)} \quad (5)$$

To find the $\kappa - \beta$ isocline for the upper glucose threshold, we set $G^* = 120$ (equal to the highest acceptable BGC) and vary I^* from $0 \mu\text{U/ml}$ to some high value ($100 \mu\text{U/ml}$ is sufficient); thus, κ and β become parametric functions with respect to I^* . This isocline is depicted in Figure 6 by the line that separates Regions I and IV from regions II and III (the “glucose concentration threshold”). All values of β and κ in the fasting case yield average glucose concentrations above 80mg/dl , so we do not show a similar curve for this lower glucose threshold.

Next, we want to determine which β and κ values yield oscillatory solutions. We solve numerically for which β and κ make the real part of the dominant eigenvalue calculated in Equation (3) equal to zero, indicating a change in sign in that eigenvalue's real part. The result is depicted in Figure 6, with the line that separates Regions I and II from Regions III and IV (the “oscillation threshold”).

Let us now take a closer look at Figure 6. In Regions III and IV we can expect blood glucose oscillations, and in Regions II and III we will observe blood glucose concentrations in an acceptable range (i.e. $G^* < 120\text{mg/dl}$). So, for a patient to have a healthy (non-diabetic) glucose and insulin profile, he or she should have physiological parameters κ and β that graphically would appear in Region III.¹

When we introduce nutrition (external glucose input), we anticipate needing tighter requirements on the parameters to maintain a healthy average blood glucose concentration and stable glucose oscillations. We account for

¹We here omit β values less than 0.05. For such low β , pancreatic disability is so acute that the clinical diagnosis would likely be type I diabetes, which we consider separately at the end of this section. Mathematically, a singularity lies in this parameter range that makes numerical solutions difficult to identify.

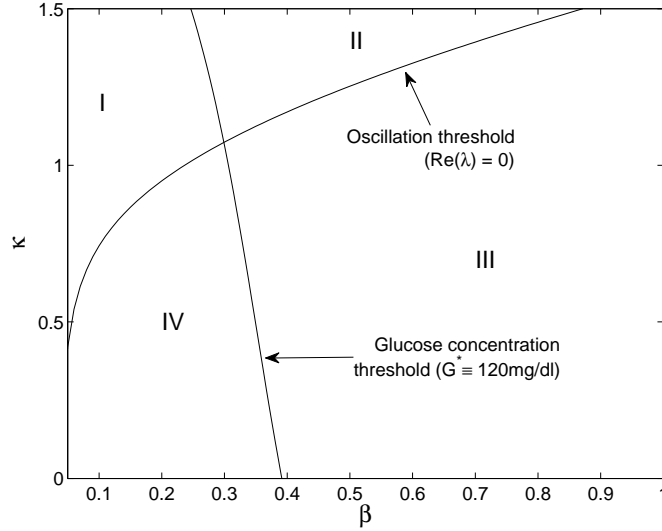


Figure 6: Separation of the parameter space under fasting conditions ($G_{in} = 0$) yielding (I) stable, hyperglycemic solutions; (II) stable, euglycemic solutions; (III) oscillatory, euglycemic conditions; and (IV) oscillatory, hyperglycemic conditions. The oscillation threshold line corresponds to the β and γ values that make the real part of the dominant eigenvalue equal to zero. The glucose concentration threshold line corresponds to the β and γ values that hold blood glucose concentration fixed at the upper threshold of 120mg/dl.

nutrition in the model by setting $G_{in} = 1.08\text{mg/dl}$ (following Li et al. [21]) and repeating the above analysis. The result is a similar partition of the parameter space, depicted in Figure 7. Here, Regions II* and III* give solutions in which the steady state glucose concentration is less than 120mg/dl, and Regions I* and II* give stable glucose oscillations.

Ideally, we would like to know which physiological parameter values will give a person a healthy blood glucose profile in both the fasting and exogenous glucose input cases. To illustrate where these parameters should lie, we can overlay the plots in Figures 6 and 7 and mark the region for which both the fasting and the nutrition circumstances predict stable oscillatory glucose concentrations below 120mg/dl. This information is depicted by the shaded region in Figure 8. We observe that if a patient's pancreatic efficiency β , insulin sensitivity γ , and physical activity m can be adjusted through medication and exercise so that they lie in this region, the patient's diabetes will be sufficiently controlled. We also note that this region fills only a portion of the larger region that would give rise to healthy average blood glucose concentrations while ignoring ultradian oscillations; that is, simply reducing a diabetic person's blood glucose levels to a normal range, as is the goal of current treatment strategies, may not be enough to induce the oscillations that are characteristic of a healthy blood-glucose profile.

For one more illustration, let us show how insulin therapy might assist a patient's treatment strategy. We might expect that insulin therapy will reduce the need for a well-functioning pancreas (i.e. β can be lower), but the effect on insulin sensitivity (κ) is more difficult to predict. To address this point, we introduce constant insulin infusion into the model at a rate of $I_{in} = 0.2\mu\text{U/ml}\cdot\text{min}$ and again determine which β and κ values yield oscillatory glucose concentrations in a healthy range under fasting and constant nutrition. We depict these results in Figure 9. As predicted, we see that incorporating insulin therapy makes possible a healthy glucose profile at lower β values. However, the region shrinks in the κ -direction, suggesting that with insulin therapy a patient will need to maintain even tighter control over their insulin sensitivity through some combination of exercise and medication.

3.2. Type I diabetes

In the case of type I diabetes, the pancreas is incapable of producing insulin (i.e. $\beta = 0$), and so healthy glucose levels can only be maintained through the injection of external insulin. It is not possible to induce stable glucose

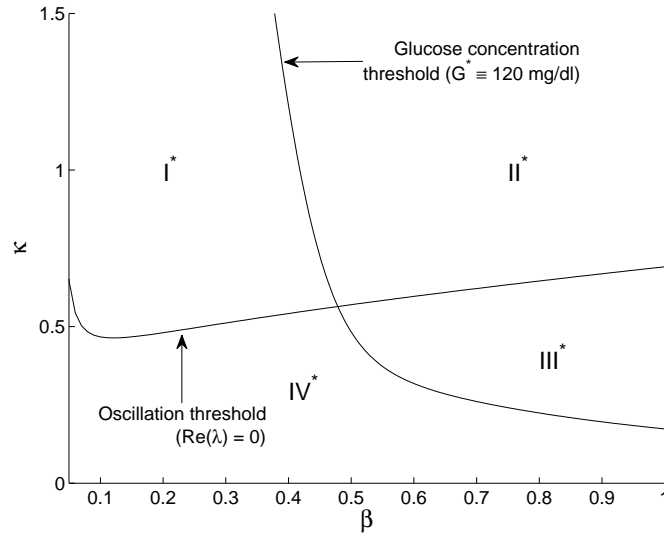


Figure 7: Separation of the parameter space under constant nutrition conditions ($G_{in} = 1.08$) yielding (I) oscillatory, hyperglycemic solutions; (II) oscillatory, euglycemic solutions; (III) stable, euglycemic conditions; and (IV) stable, hyperglycemic conditions. The oscillation threshold line corresponds to the β and γ values that make the real part of the dominant eigenvalue equal to zero. The glucose concentration threshold line corresponds to the β and γ values that hold blood glucose concentration fixed at the upper threshold of 120mg/dl

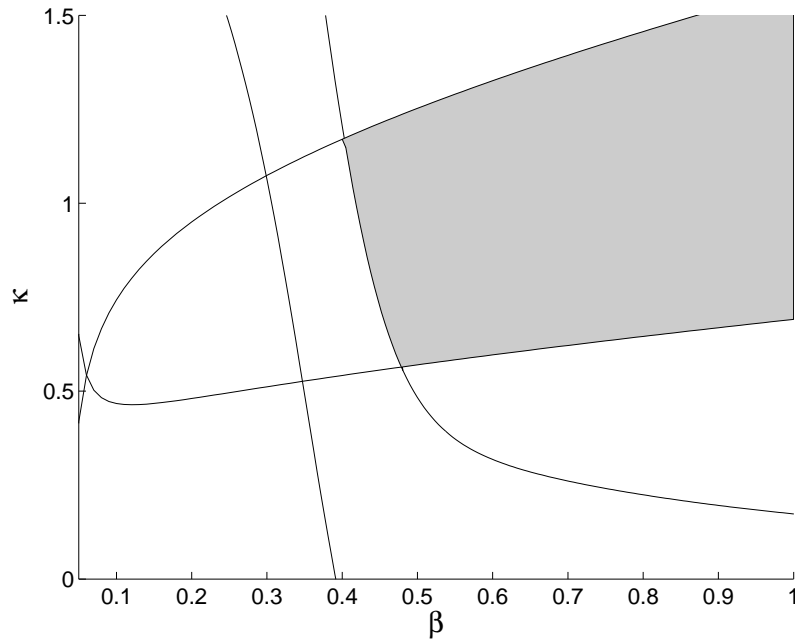


Figure 8: Overlay of fasting and constant-nutrition region plots (Figures 6 and 7). The shaded area indicates parameter values that yield oscillatory glucose concentrations in a healthy range for both fasting and constant nutrition.

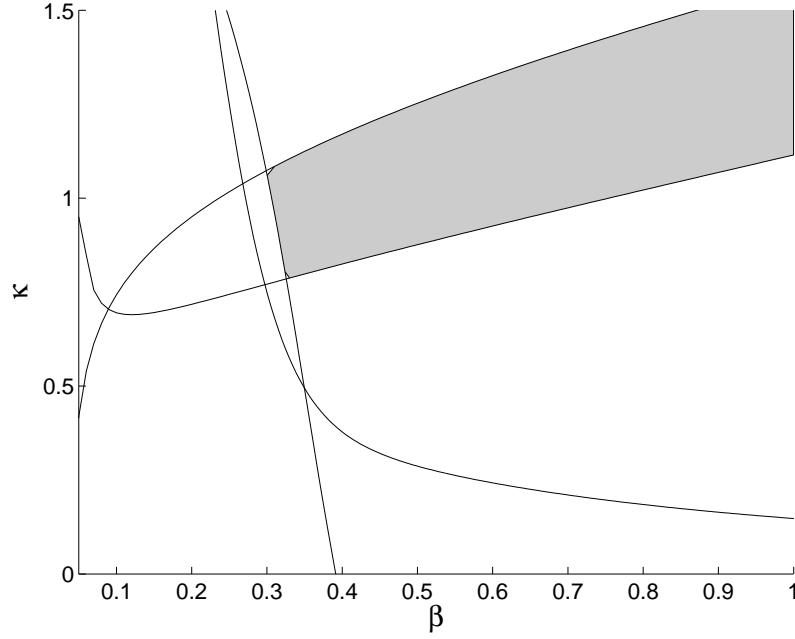


Figure 9: Overlay of fasting and constant-nutrition region plots with insulin therapy ($I_{in} = 0.2 \mu\text{U}/\text{ml}\cdot\text{min}$). The shaded area indicates parameter values that yield oscillatory glucose concentrations in a healthy range for both fasting and constant nutrition.

oscillations under these conditions, but we can still determine how much insulin is required to keep glucose within a range of 80-120mg/dl. Starting with the steady state relation

$$0 = G_{in} - f_2(G^*) - \kappa f_3(G^*)f_4(I^*) + f_5(I^*)$$

$$0 = I_{in} - \frac{V_{max}I^*}{K_M + I^*}$$

we can solve for κ and I_{in} as follows:

$$\kappa = \frac{G_{in} - f_2(G^*) + f_5(I^*)}{f_3(G^*)f_4(I^*)} \quad (6)$$

$$I_{in} = \frac{V_{max}I^*}{(K_M + I^*)} \quad (7)$$

As before, we first consider the fasting case, where $G_{in} = 0$. Holding G^* fixed at 80mg/dl and 120mg/dl and treating I^* as a parametric variable we can outline a region in which, for a given κ , we can find how much insulin (I_{in}) is required to maintain a healthy blood glucose concentration. We can repeat this process with the “full nutrition case” where $G_{in} = 1.08\text{mg}/\text{dl}\cdot\text{min}$, producing a second such region that gives the required insulin when a person receives nutrition. These regions are depicted in Figure 10. The lighter area between the regions depicts the insulin infusion rates that would be effective when glucose intake is somewhere between fasting and full nutrition. As one might expect, the amount of insulin required increases sharply when the body’s insulin sensitivity (κ) becomes low.

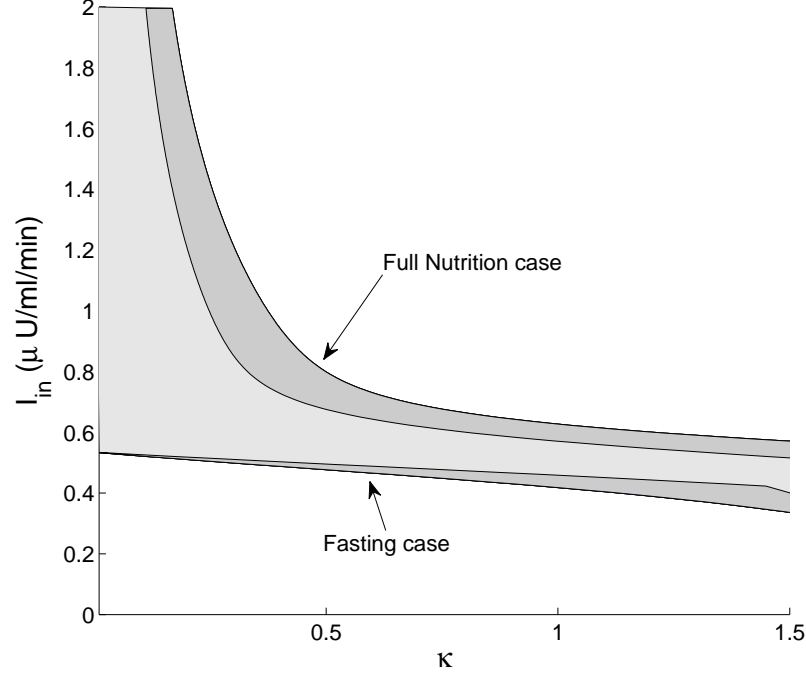


Figure 10: This plot indicates how much insulin is required for a type I diabetic to maintain a healthy BGC given insulin sensitivity κ . The dark upper band indicates the insulin infusion rates that will keep a type 1 diabetic's BGC at an acceptable level with "full nutrition" ($G_{in} = 1.08 \text{ mg/dl} \cdot \text{min}$). The dark lower band indicates the insulin infusion rates necessary to keep a fasting type 1 diabetic's BGC at an acceptable level ($G_{in} = 0$). The lighter region in between the two bands corresponds to the insulin required to maintain an acceptable BCG for nutrition levels between fasting and full.

4. Hypothetical case studies

4.1. Type II diabetic treatment

To illustrate the value of the analysis in Section 3, let us consider a hypothetical type II diabetic. The patient's fasting glucose is measured at 130 mg/dl , higher than the ADA's 125 mg/dl threshold for diabetes diagnosis (American Diabetes Association [4]). The patient's doctor measures the patient's pancreatic efficiency and insulin sensitivity using a euglycemic glucose clamp or an oral glucose tolerance test and the *minimal model*, two techniques that have been used in the past to characterize a patient's disease (Bergman [6], Brun et al. [8], Ferrannini and Mari [15], Stumvoll et al. [29]). Results show that the patient's pancreas functions at 30% of normal efficiency and that the patient's insulin sensitivity is 40% that of an average non-diabetic person. The patient lives a largely sedentary life, so the amount of moderate to physical activity per day the patient receives (m) is virtually zero. From this information, the doctor can readily deduce the parameter values $\beta = 0.3$ and $\kappa = 0.4 \cdot [1 + 0.0072 \cdot (0 - 60)] = 0.23$. Figure 11 shows the model's prediction of the patient's glucose and insulin profile; note that the patient is certainly hyperglycemic, since the patient's blood glucose concentration regularly exceeds 130 mg/dl . By placing the patient's particular β and κ values on the plot in Figure 8 it becomes apparent that the patient requires an increase in both pancreatic efficiency and insulin sensitivity. There are now several options that could help re-establish glycemic control. To increase the patient's insulin sensitivity, the doctor could place the patient on a medication such as Metformin that would increase γ to 0.7, along with introducing 60 minutes of physical activity per day (Kirpichnikov et al. [19]). Then, to decrease the patient's BGC, the doctor could increase the patient's pancreatic efficiency β to 0.6 using sulfonylurea drugs (Aguilar-Bryan et al. [1]). The model's prediction for this scenario is depicted in Figure 12. Alternatively, the doctor could prescribe insulin therapy in the form of $0.2 \mu\text{U/ml} \cdot \text{min}$ administered continuously by an artificial pancreas; then, the patient's pancreatic efficiency would only have to increase to about 0.4 through the use

of sulfonylureas. An additional 60 minutes of daily exercise would increase the patient's insulin sensitivity enough to give the patient a healthy blood glucose profile, depicted in Figure 13. This example illustrates how, with proper verification and validation, our analysis and proposed model could help characterize a specific individual's disease and inform medical care. Our results make it easy to consider multiple treatment options involving medication, changes in lifestyle, and/or medical technology, allowing the patient to choose the lifestyle changes and therapies that work best him or her.

4.2. Type I diabetic treatment

Let us now consider a different patient, a type I diabetic ($\beta = 0$) whose insulin sensitivity is about 75% that of an average non-diabetic person ($\gamma = .75$), and who receives about an hour of exercise per day ($m = 60$). Figure 14 shows this patient's glucose and insulin profiles in the absence of treatment; with a fasting steady state BGC greater than three times the ADA-suggested upper value, an intervention is clearly necessary. Figure 14 also includes a phase portrait of the glucose and insulin concentrations, demonstrating clear stable oscillations. Similar phase portraits arise from the remaining glucose-insulin profiles that will be presented, and are omitted here. To make use of the information depicted in Figure 10, the patient's doctor could first calculate the patient's particular κ -value; in this case, $\kappa = 0.75[1 + 0.0072(60 - 60)] = 0.75$. From Figure 10, we see that an insulin infusion rate between 0.45 and 0.7 $\mu\text{U}/\text{ml}\cdot\text{min}$ from an artificial pancreas could adequately control the patient's BGC, depending on the patient's glucose intake rate. Figure 15 depicts the patient's glucose and insulin profiles with full nutrition ($G_{in} = 1.08$) and an insulin infusion rate of $I_{in} = 0.65\mu\text{U}/\text{ml}\cdot\text{min}$; with a BGC of 100 mg/dl , the patient's glucose levels are adequately controlled.

5. Conclusions and Future Work

With this work, we have provided the necessary tools to identify personalized treatment strategies for diabetic patients based on current clinical recommendations. We have furthermore shown that common treatment strategies may omit the ultradian glucose oscillations normally observed in healthy individuals, and so we lay a framework to ensure that these oscillations are also maintained. In particular, we have shown that a type II diabetic's blood glucose levels should be adequately controlled and oscillations will be maintained when the patient gets an hour of daily exercise and is placed on a combination of Metformin and sulfonylurea drugs to increase his or her insulin sensitivity and pancreatic efficiency, respectively, to 70% and 60% of normal. Insulin therapy and an additional hour of exercise reduce the patient's need for sulfonylureas, requiring those drugs to increase the patient's pancreatic efficiency to only 40% of normal. Similarly, we have proposed that a particular type I diabetic's blood glucose levels can be properly controlled with a constant insulin infusion between 0.45 and 0.7 $\mu\text{U}/\text{ml}\cdot\text{min}$, if the patient takes in glucose at a constant rate. With proper verification, the model presented here could serve as a valuable clinical tool, helping to provide diabetic patients with a range of treatment options.

This work builds upon a foundation of previous models of the human glucose and insulin system. Of particular note are those by Sturis et al. [30], who presented the foundational model of the system; Drozdov and Khanina [14] who first incorporated a time delay to account for the lag in hepatic glucose production; and Li et al. [20] who incorporated a second time delay to account for the lag in insulin release, and who established the model most closely associated with the one we present here. Makroglou et al. [23] provide a detailed summary of these and other important models in the field. The work we present marks a shift in focus from much of what precedes it; the existing literature largely emphasizes the effect of the two time delays on system's stability, but little has been done to explicitly analyze the effects of medication and exercise (Giang et al. [16], Li and Zheng [22], Pei et al. [25]). By explicitly accounting for these factors, we hope to shrink the gap between theoretical models and clinical practice, providing individualized information that can inform clinical care, and to help guide the production of personalized medical technology.

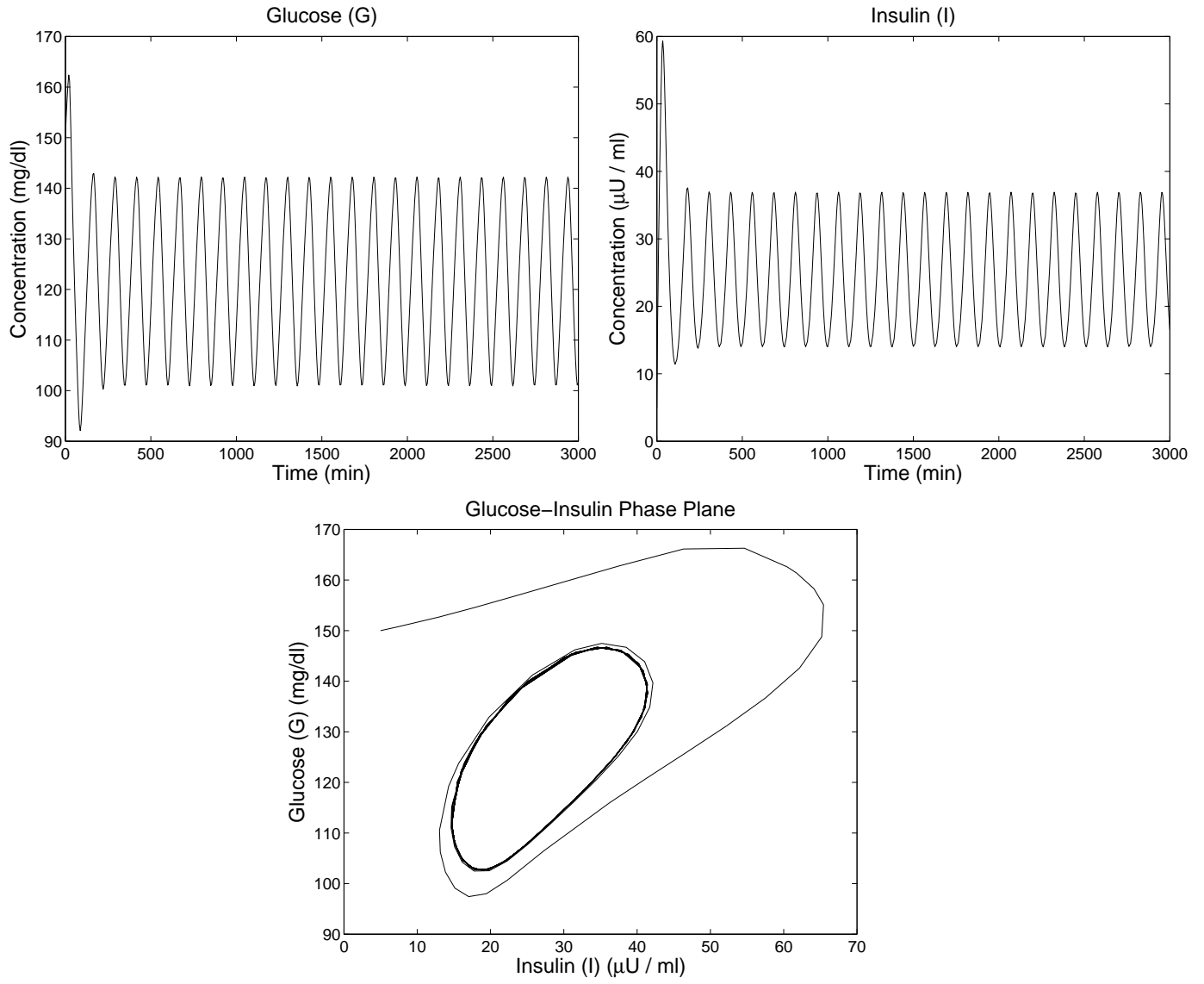


Figure 11: Glucose and insulin profiles and phase plane for a type II diabetic with no treatment ($G_{in} = 0$, $I_{in} = 0$, $\tau_1 = 5$, $\tau_2 = 15$, $\beta = .3$, $\gamma = .4$, $m = 0$, $V_{max} = 150$, $K_M = 2300$)

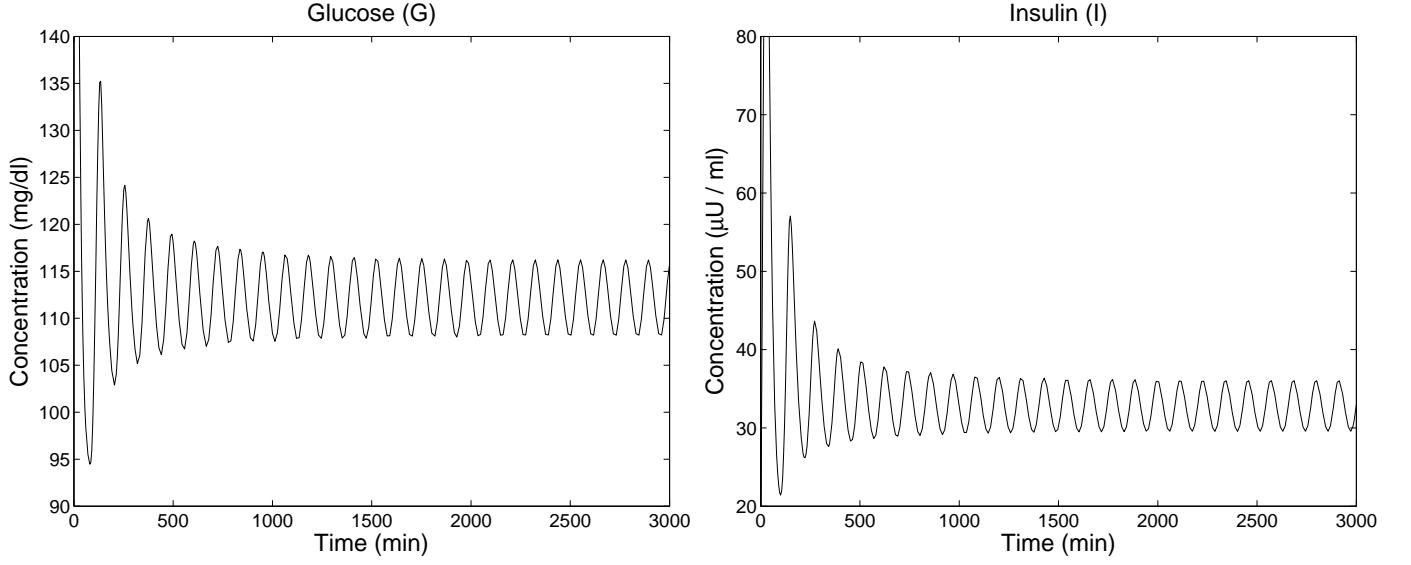


Figure 12: Glucose and insulin profiles for a type II diabetic under the first treatment strategy ($G_{in} = 1.08$, $I_{in} = 0$, $\tau_1 = 5$, $\tau_2 = 15$, $\beta = .6$, $\gamma = .7$, $m = 60$, $V_{max} = 150$, $K_M = 2300$)

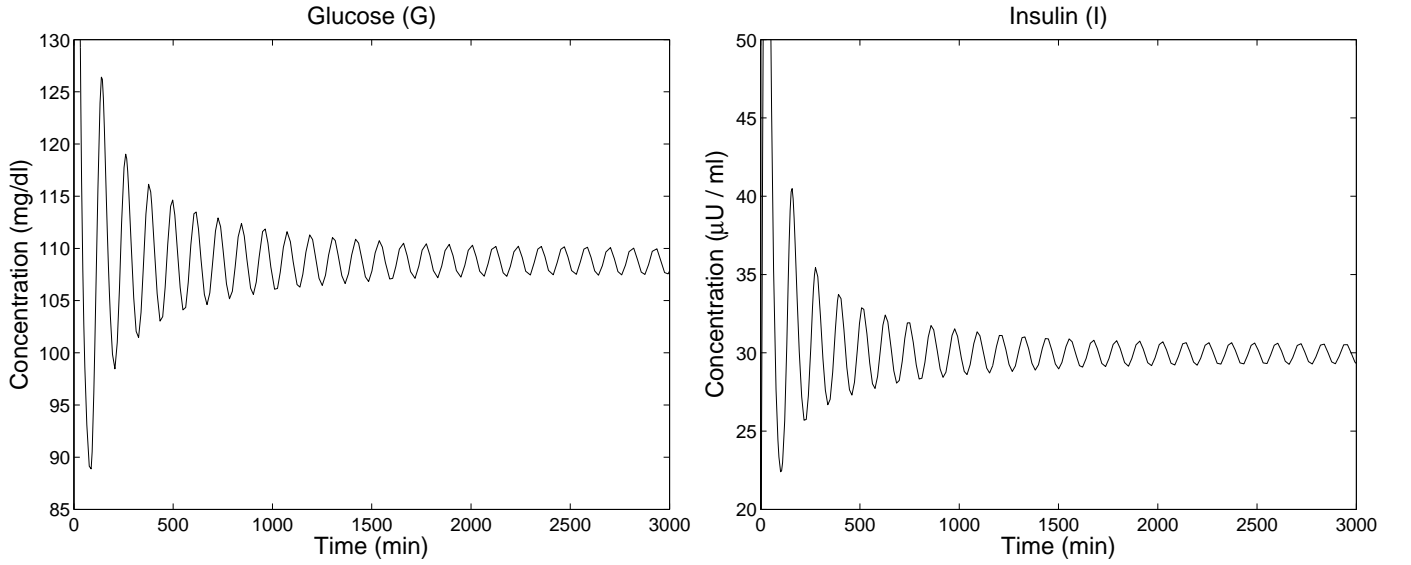


Figure 13: Glucose and insulin profiles for a type II diabetic under the second treatment strategy ($G_{in} = 1.08$, $I_{in} = 0.2$, $\tau_1 = 5$, $\tau_2 = 15$, $\beta = .4$, $\gamma = .7$, $m = 120$, $V_{max} = 150$, $K_M = 2300$)

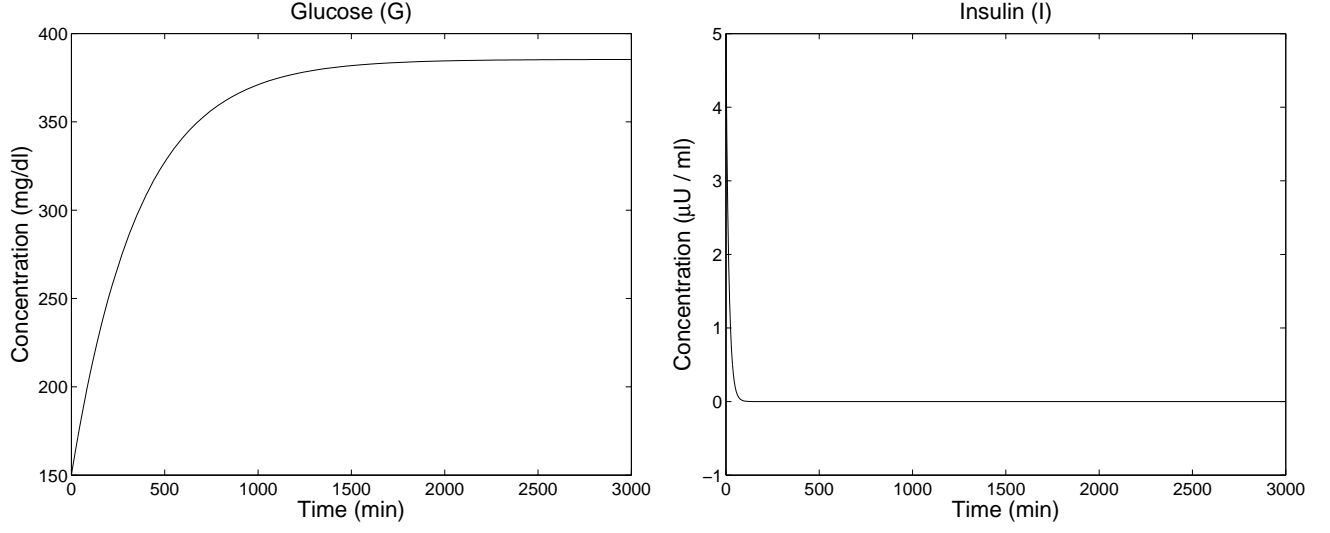


Figure 14: Glucose and insulin profiles for a type I diabetic with no treatment ($G_{in} = 0$, $I_{in} = 0$, $\tau_1 = 5$, $\tau_2 = 15$, $\beta = 0$, $\gamma = .75$, $m = 60$, $V_{max} = 150$, $K_M = 2300$)

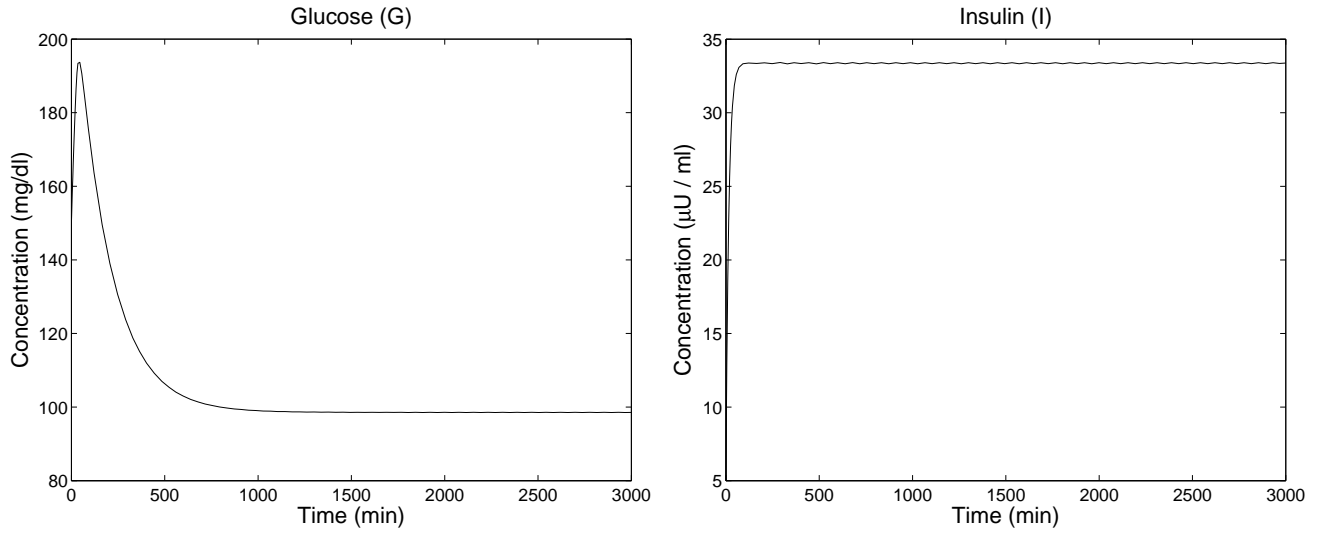


Figure 15: Glucose and insulin profiles for a type I diabetic with insulin therapy ($G_{in} = 1.08$, $I_{in} = 0.65$, $\tau_1 = 5$, $\tau_2 = 15$, $\beta = 0$, $\gamma = .75$, $m = 60$, $V_{max} = 150$, $K_M = 2300$)

Our next steps will involve accounting for non-constant glucose infusion from meals and for periodic insulin infusion due to injection, in order to more closely represent the day-to-day variability in a diabetic person's glucose and insulin intake. We note that, following previous work in this field, our model does not explicitly account for the effect of glucagon. While this does not seem to negatively impact the model's ability to replicate the human glucose regulatory system, our next models might achieve even better physiological correspondence by accounting for this additional hormone. We also note that other organs, such as the kidneys, supplement the liver's glucose production. Accounting for these organs' effects in future models might yield further insights into the onset of blood glucose oscillations and could broaden treatment options. We then plan to develop an algorithm to determine precisely when and how much insulin should be injected to maintain a diabetic person's BGC in a healthy range, given their activity levels, pancreatic efficiency, and insulin sensitivity. We envision applying this algorithm to an artificial pancreas which, with a small amount of initial programming and information from an embedded accelerometer, would require minimal user input. A recent review of existing devices calls for "smart control algorithms" for that better control glucose and insulin oscillations; we anticipate that this work will respond directly to that call (Cobelli et al. [11]). The development of such a device would undoubtedly allow people with diabetes to live freer, simpler, and healthier lives.

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